Original article

The treatment of primary hypertension

Twelfth of a series on drug therapy

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■ Atherosclerosis, first, and hypertension, second, constitute the most common therapeutic problems of our time, considerably outranking cancer in incidence. Whereas little progress has been made in reducing the mortality rate from atherosclerosis or cancer, deaths from hypertension have fallen significantly over the past fifteen years, and the favorable trend is continuing.

Antihypertensive drugs were developed during the 1950s and it is tempting to ascribe these encouraging trends in mortality to advances in specific therapy. However, it must be recognized that mortality figures may change as a result of other factors, and it is, therefore, prudent to seek out additional supporting evidence.

Prevention of organic complications

Hypertensive complications. What effect does reduction of blood pressure have on preventing the organic complications that are commonly associated with hypertension? In considering this question, it is convenient to separate those complications which are associated specifically with hypertension from those which are due primarily to atherosclerosis.

The available evidence suggests that hypertensive complications are the result of stresses placed on the heart and blood vessels by the elevated blood pressure. The predominant effect on the vascular system is sclerosis of the arterioles, and on the heart, left ventricular hypertrophy and dilatation.

There is convincing evidence that any form of treatment which lowers blood pressure is effective in improving and preventing hypertensive congestive heart failure. Cardiac failure has fallen from a major to a minor cause of death in adequately treated hypertensive patients.

Reduction of blood pressure also has been shown to be effective in the treatment of acute, severe, hypertensive states. Antihypertensive therapy will revert malignant hypertension to the benign phase. Hemorrhages, exudates, and papilledema in the optic fundi gradually disappear when the blood pressure is effectively lowered. If renal damage is not severe, patients may lead productive lives for many years with continued treatment.

Since antihypertensive treatment reverses the accelerated phase of hypertension, it follows that the transition from benign to malignant hypertension also should be prevented in adequately treated patients. This assumption is supported by the observation that the incidence of malignant hypertension appears to be very low in patients receiving continuous antihypertensive therapy.

In addition to preventing malignant hypertension, antihypertensive therapy has practically eliminated the occurrence of acute hypertensive encephalopathy. Also, clinical trials comparing treated with nontreated patients have shown that cerebral hemorrhage is significantly less frequent in treated patients.

Nephrosclerosis. Sclerosis of arterioles is the primary small vessel lesion related to hypertension, the principal target organ being the kidney. The fulminant type, characterized by arteriolonecrosis, is effectively prevented by antihypertensive therapy. Nephrosclerosis without necrosis, however, occurs in patients with essential hypertension and progresses at a much slower pace. Because of this slow progression it has been difficult to demonstrate a favorable effect of antihypertensive treatment. There is, however, indirect evidence favoring the view that lowering blood pressure may retard the rate of development of nephrosclerosis.

Atherosclerotic complications. The most important atherosclerotic complications are myocardial infarction and cerebrovascular thrombosis, which have now risen to first and second place as the major causes of death in hypertension, replacing congestive heart failure, cerebral hemorrhage, and uremia. This change in incidence may be due in part to the fall in death rate from the latter complications. However, it also is probable that hypertensive patients who are saved by drug

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treatment from the fulminant effects of severe hypertension may now live long enough to develop the atherosclerotic complications.

It is well established that hypertension is a significant risk factor in the genesis of atherosclerosis. The available evidence suggests that the elevated arterial pressure per se predisposes the arterial walls in some unknown way to the deposition of atherosclerotic plaques. Such considerations suggest that blood pressure should be lowered to normal in the early stages of hypertension in order to prevent the future development of atherosclerosis.

Estimating prognosis and need for treatment

Lability in hypertension. Since many of the complications of hypertension appear to be related directly to the elevated blood pressure, it is reasonable to assume that the extent of the pathological changes will depend on both the height of the blood pressure and its duration. If the blood pressure is high for only brief periods of time, significant vascular pathology might not be anticipated. This precept is borne out by a number of studies indicating that morbidity and mortality rates are considerably higher in so-called fixed hypertension than in the labile form. Patients whose hypertension is initially labile may later develop fixed hypertension in middle age.

Differentiation between the two groups is not possible on the basis of recordings of blood pressure in the physician's office. Individuals who remain labile may, in middle and old age, exhibit high pressures during a visit to a doctor's office and still be normotensive during normal daytime activities at home or work. Such individuals often exhibit little or no evidence of organic damage. Other hypertensive patients exhibit elevation of blood pressure throughout the day, even when they are at home or are hospitalized. The majority of these patients exhibit organic changes, the rate of progression varying in general with the height of the diastolic blood pressure. Thus, in evaluating hypertensive patients for treatment, it should be recognized that it is not only the height of the blood pressure which is important but also its persistence. When blood pressure is measured only in the office or clinic it is difficult, if not impossible, to differentiate between the fixed and labile forms of hypertension.

Determination of lability. In determining the "basal" blood pressure it is essential to repeat the recording procedure frequently enough so that the alarm reaction wears off. This can be accomplished by hospitalization for three or four days with recordings taken by the nursing staff four or five times daily. The patient is encouraged to be up and about the hospital ward during this period.

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For outpatients, the recording of blood pressure at home by the patient or a member of his family is the most practical method of estimating the basal blood pressure. The physician should have available a spare manometer which can be loaned to the patient. The office nurse instructs the patient or, preferably, a member of his family in the proper technique of blood pressure recording. Twice-daily recordings for a period of two weeks are sufficient to provide an indication of the average blood pressure. The readings can be taken at the beginning and end of the day so as not to interfere with normal work schedules. A record is kept which is presented to the physician at the next office visit.

Some physicians fear that such emphasis on blood pressure levels and open disclosure of the readings may induce a "manometric neurosis." Experience has shown, however, that in the majority of patients the procedure soon loses its capacity for promoting apprehension when frequently and routinely repeated. Further, the patient should be reassured that if the blood pressure remains elevated it can be effectively controlled by antihypertensive treatment.

Extent of organic damage. In addition to the assessment of basal blood pressure, the extent of the organic damage present at

the time of the initial evaluation of the patient also is of great value in estimating the prognosis and, hence, the need for treatment.

The important organ systems that are affected in hypertension are the central nervous system including the optic fundi, the heart plus aorta, and the kidneys.

In the *optic fundi,* vascular changes are characterized by arteriolar tortuosity, widening of the light reflex, arteriovenous nicks, and irregularity of arteriolar caliber. Since the larger vessels close to the optic disk may exhibit some of these changes in normal individuals, inspection of the blood vessels two disk diameters or more peripheral to the nerve head provides more reliable criteria of vascular pathology. Because of the wide range of normal variation, great emphasis should not be placed on minor vascular changes.

Hemorrhages, soft exudates, or papilledema indicates that generalized arteriolar damage is occurring at an accelerated rate. The hemorrhages are flame-shaped or striate rather than round and occur near the disk. Other causes for hemorrhages such as diabetes and anemia should be ruled out. Soft fluffy exudates, generally occurring close to the main vessels within three diameters of the disk, are characteristically seen in patients with severe hypertension. Smaller, sharply defined, hard exudates also occur and persist for longer periods following treatment. The presence of hemorrhages, soft exudates, or papilledema indicates the need for immediate hospitalization and intensive treatment in order to arrest the rapid progression of vascular damage.

In the *central nervous system* the most frequent complication is a stroke. Although patients who recover from a cerebral hemorrhage or thrombosis may live for many years thereafter, especially if the blood pressure is well controlled, the prognosis is more guarded than if such complications had not occurred. Similarly, patients with acute hypertensive encephalopathy may survive for long periods, providing renal function is adequate and the blood pressure is vigorously controlled. On the other hand, subarachnoid hemorrhage carries an uncertain prognosis unless the cause of the subarachnoid bleeding can be identified and repaired surgically. Morning occipital headache often is a symptom of severe hypertension, but headache in other locations or dizzy spells have no prognostic value.

The *heart* responds to sustained hypertension with hypertrophy or dilatation which often can be detected by X-ray and electrocardiography. In the physical examination, a forceful and prolonged apical impulse and a presystolic gallop may be detected. The frequent superimposition of coronary atherosclerosis may lead to angina or to increased susceptibility to develop congestive heart failure.

An additional useful sign is the degree of aortic dilatation and unfolding visualized in the chest X-ray. In the physical examination, tortuous and dilated peripheral arteries, such as the subclavian or the brachial, indicate that severe, sustained hypertension has been present for some time.

The status of the *kidneys* has great prognostic importance. Minor degrees of renal damage, however, cannot be detected by routine clinical methods. Lack of concentrating ability and retention of phenolsulfonphthalein indicate significant impairment, while nitrogen retention reflects far-advanced renal deterioration.

In the presence of a moderate degree of azotemia, antihypertensive therapy may still be of value, if effectively and judiciously applied. However, the prognosis is much more guarded than if effective measures had been taken at an earlier date. In the terminal stage of renal failure with elevation of BUN above 100 mg. percent, antihypertensive therapy usually is of little value. When the uremia is accompanied by severe congestive heart failure, moderate reduction of blood pressure may be helpful in controlling symptoms.

Age and sex. Other aids in estimating the prognosis and, hence, the need for treatment include the age and sex of the patient. Young patients are more apt to develop accelerated hypertension. Atherosclerotic complications also tend to occur at a relatively early age. The untreated patient who exhibits an elevation of basal blood pressure before age 35 has a greatly increased risk of dying before age 55 as compared to a normal individual. In addition, numerous studies have shown that the mortality rate is higher in hypertensive men than in women. Other conditions being equal, a young man with hypertension should be more aggressively treated than other patients.

In summary, the purpose of the prognostic evaluation is to decide on the need for and type of medical treatment. The work-up should include an estimate of basal blood pressure and an assessment of the degree of organic damage. The history and physical examination should be directed

especially toward the principal target organs in hypertension, namely, the optic fundi, central nervous system, heart, and kidneys.

Laboratory tests should include a chest X-ray and electrocardiogram, urinalysis, phenolsulfonphthalein excretion, and BUN or serum creatinine. If thiazide diuretics are to be used in treatment, the fasting blood sugar, serum potassium, and serum uric acid should be included. Additional important tests which are helpful in screening patients for curable forms of hypertension are the intravenous pyelogram and, when available, radioisotope renogram and renal scan for renovascular hypertension; the twenty-four-hour urinary excretion of vanylmandelic acid (VMA) for pheochromocytoma; and the serum potassium level for primary aldosteronism.

Choice of drug treatment

Although there are several hundred preparations that are marketed for the treatment of hypertension, the useful drugs of proved value make up only a relatively small number. These are [1] the natriuretic agents, [2] rauwolfia alkaloids, [3] hydralazine, [4] methyldopa, and [5] the sympathetic blocking drugs such as guanethidine and pargyline.

Natriuretic agents. Chlorothiazide (Diuril®) and related agents are useful in all forms of hypertension. In patients with mild hypertension, they may effectively control blood pressure without additional therapy. In patients with more resistant disease, the natriuretic agents enhance the activity of the other antihypertensive drugs.

While the mechanism of the antihypertensive activity of the thiazides is still in some dispute, it is most likely associated with sodium depletion. The various compounds differ primarily with regard to dose and duration of action, no one agent being superior in antihypertensive effectiveness or in toxicity.

Effective antihypertensive doses of representative natriuretic agents are as follows: chlorothiazide, 250 to 500 mg. twice daily; hydrochlorothiazide (Hydro-Diuril®, Esidrex®), 25 to 50 mg. twice daily; and chlorthalidone (Hygroton®), 50 to 100 mg. once daily. Except in severe hypertension, treatment generally is initiated at the lower dose level and is increased to the higher level if the blood pressure is not controlled.

Among the side effects of these drugs, the most frequent are hypokalemia and hyperuricemia. Hypokalemia seldom is troublesome except in patients who are losing potassium from other causes or who are taking digitalis. Hypokalemia increases the incidence of toxic arrhythmias produced by the digitalis alkaloids. In patients who require digitalis, mixtures of spironolactone and hydrochlorothiazide (Aldactazide®) or of triameterene and hydrochlorothiazide (Dyazide®) are indicated.

Hyperuricemia occurs in approximately 40% of thiazide-treated patients. In susceptible individuals, persistent hyperuricemia can lead eventually to gout. It is not surprising, therefore, that the incidence of acute gouty arthritis has increased significantly in patients receiving thiazides. Since thiazide-induced hyperuricemia can be controlled with 0.25 to 0.5 gm. of probenecid (Benemid®) twice daily, treatment with the latter drugs may be indicated in patients who develop elevated levels of serum uric acid.

Although thiazides lower carbohydrate tolerance and on rare occasions precipitate acute hyperglycemic attacks, there is little evidence to support the view that they produce permanent diabetes. The incidence of diabetes seems to be no higher in thiazide-treated patients than in control groups of similar age. In addition, the presence of diabetes is not an absolute contraindication to treatment with thiazide diuretics.

Rauwolfia alkaloids. Reserpine is the alkaloid usually employed, there being no convincing evidence that other rauwolfia alkaloids are superior. The antihypertensive effect is mediated through partial depletion of catecholamines. The usual dose is 0.5 to 1 mg. daily for two weeks followed by a maintenance dose of 0.1 to 0.5 mg. Higher maintenance doses are not advisable because of a considerable increase in the incidence of toxicity.

The most important side reaction is the development of a severe and even suicidal mental depression. It is advisable to warn the patient or a member of the family of this possibility. The symptoms are early morning insomnia, anxiety, despondency, and anorexia. True depression should be distinguished from mild lethargy and loss of drive which occurs fairly frequently with reserpine. Other common side effects are nasal stuffiness, slight diarrhea, increased appetite, and nightmares.

Because of the limitation on dosage imposed by the risk of side effects, the antihypertensive effectiveness of reserpine used alone is somewhat limited. However, the drug is often quite effective when added to a regimen con-

taining thiazides. The latter drugs enhance the mild antihypertensive activity of reserpine even when it is maintained at rather low-maintenance dose levels, such as 0.25 mg. daily.

Hydralazine. Hydralazine (Apresoline®) is useful only as an adjunct to either thiazides or reserpine or both. The initial dose is 10 to 25 mg. two to three times daily, which can be increased to 50 mg. three times daily if necessary. Doses above 150 mg. daily are not advisable because of the risk of developing the lupus erythematosus syndrome at higher doses. The syndrome resembles disseminated lupus with arthritis, dermatitis, and renal lesions. In the recommended lower dose range the principal side effects are headache and palpitation.

Methyldopa. Although often well tolerated, methyldopa (Aldomet®) is more likely to produce orthostatic hypotension than the agents described above. The orthostatic hypotension is less severe, however, than with guanethidine or pargyline. The effective dose range of methyldopa varies between 250 and 750 mg. three to four times daily.

An important toxic effect of methyldopa is hepatitis. This reaction usually occurs within the first six weeks of treatment and generally is mild. Fever or malaise are the leading symptoms and elevation of SGOT is the most frequent laboratory abnormality. Recovery is rapid after discontinuation of the drug.

The development of a positive Coombs test and hemolytic anemia have recently been ascribed to methyldopa. In addition to orthostatic hypotension, other common side effects include sleepiness, which often is transient, and dry mouth.

Guanethidine and pargyline. Guanethidine (Ismelin®) generally is reserved for patients whose hypertension is severe and resistant to other antihypertensive drugs. Guanethidine induces a peripheral block of the sympathetic nervous system, thereby producing a decrease in blood pressure and heart rate. The duration of action is long and doses are cumulative over a period of several days. The effective dose varies widely in different patients from as little as 10 mg. to as much as 200 mg. daily. In most patients, however, the effective dose with adjunctive thiazide is in the neighborhood of 20 to 60 mg. per day. Because of the risk of syncope due to orthostatic hypotension, the drug should be started at 10 mg. once daily, preferably with thiazides, and increased gradually by 10 mg. increments until the optimal reduction of blood pressure is achieved within the limits imposed by orthostatic symptoms. More rapid titration can be carried out in the hospital where the blood pressure can be checked frequently in both the supine and upright positions.

Other common side effects of guanethidine are diarrhea, which may be controlled with atropine-like drugs but usually necessitates reduction in dosage, and retrograde ejaculation.

Pargyline (Eutonyl®), a monoamine-oxidase inhibitor, also blocks sympathetic nervous system activity, producing a reduction of blood pressure with orthostatic hypotension. Because of the incompatibilities between monoamine-oxidase inhibitors and certain other drugs, as well as the severe hypertensive reactions that follow the ingestion of processed cheese, guanethidine appears to be the safer of the two drugs for use in resistant hypertension.

Methods of treatment

Hypertension should be regarded as an essentially controllable disease. Severe restrictions on normal patterns of living seldom need be imposed. The aim of treatment is not only to control blood pressure but also to interfere as little as possible with the patient's usual working and recreational habits. The patient should not be made to feel that he is an invalid.

Hypertensive patients vary considerably in their response to individual drugs, with regard to both antihypertensive effectiveness and incidence of side effects. It often is necessary, therefore, to try a variety of drug schedules before settling on a regimen that provides the most effective blood pressure control with the least number of side effects.

In mild and moderate hypertension, treatment usually is begun with a natriuretic agent. If this is not effective, reserpine may be added, followed by hydralazine if necessary. By noting the effect of each antihypertensive agent as it is separately added, an informed judgment as to its relative efficacy in the individual patient can be made. From this experience one may arrive at the regimen best suited to the particular patient. Thus, patient A may need only a natriuretic agent, patient B will be best controlled on reserpine alone, while patient C requires a combination of drugs. Once this decision has been made on the basis of the therapeutic trial, it often is possible to use preparations containing a desired combination in a single tablet. Combination tablets should not

be used initially, however, since it is not possible to determine which of the ingredients is producing the desired effect. Obviously, it is not desirable to expose the patient for long periods of time to more medications than he actually needs.

Most patients with essential hypertension will respond to thiazide alone or to various combinations of thiazide, reserpine, and hydralazine. A few may not, and others may have side effects, necessitating a change in regimen. In such instances, methyldopa, particularly when combined with a natriuretic agent, frequently is effective and usually is well tolerated.

Methyldopa also may be effective in severe forms of hypertension particularly when renal failure is present. When the drug does not control blood pressure in severe hypertension, guanethidine should be used. Thiazides are useful adjuncts with either drug. In fact, in the presence of severe or malignant hypertension, it often is necessary to add several antihypertensive agents including thiazides, guanethidine, and methyldopa in order to achieve satisfactory blood pressure reduction. In such cases, after the blood pressure has remained under adequate control for several months, it frequently is possible to withdraw or reduce the doses of the drugs causing the most disturbing side effects. Fortunately, severe hypertension frequently tends to moderate after a period of intensive treatment so that less medication is required for adequate control.

As in diabetes, the physician's role is to guide the patient in a lifelong program of controlling his disease. The patient will be more cooperative if he is given some understanding of the purpose of the treatment and if the therapeutic regimen is flexible.

Home blood pressure recordings can be an important motivating influence. The procedure is particularly effective in convincing the patient that regularly taken medications and toleration of occasional real or imagined side effects are essential for adequate blood pressure control. Home recordings also are a valuable guide to the effectiveness of treatment, particularly when doses need to be carefully titrated, such as is the case with guanethidine. Transient escape from the effects of antihypertensive drugs often occurs during the apprehension associated with the office visit. A record of blood pressures taken in the home will prevent the physician from being misled and, hence, overdosing on the basis of the transiently elevated levels recorded in his office.

Since hypertensive patients develop atherosclerosis at an accelerated rate, additional practical measures that may delay the latter process can go hand in hand with the program of blood pressure control. Such measures may include weight reduction if indicated, partial substitution of unsaturated for saturated fats, and a program of daily moderate exercise.

Never before has the medical profession been in such an advantageous position for constructive accomplishment in the treatment of hypertension. To the physician who applies this newer knowledge wisely, the satisfactions fully justify the effort expended. The key to successful treatment is individualization of therapeutic schedules as judged by the response of each patient to treatment. ▣